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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,661	02/28/2002	Masatoshi Chiba	P21749	5687

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
05/08/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/926,661	CHIBA, MASATOSHI	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-16 and 22-28* is/are pending in the application.

4a) Of the above claim(s) *22-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 6-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks filed 11 March 2009 have been entered. No claims have been amended, added, or canceled. Claims 1, 3 - 4, 6 - 16, and 22 - 28 are pending.

Election/Restrictions

2. Claims 22 - 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 28 July 2005.

3. Claims 1, 3 - 4, and 6 - 16 are under examination.

Maintained Rejections

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4, and 6 – 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka (WO 97/02832, published 30 January 1997, of record) in view of Yamahira (U.S. Patent 4,244,943, issued 13 January 1981).

As set forth previously, Tanaka U.S. Patent Application Publication 2001/0051604 is the published version of the national stage entry of the PCT application that was published as WO 97/02832) as a translation of Tanaka WO 97/02832. The page and paragraph numbers cited

herein are from the '604 publication but the same information was disclosed in Japanese in the earlier WIPO publication.

This rejection is maintained for the reasons previously made of record. The places in each of the references where the various claim limitations are disclosed were set forth in the office action mailed 19 September 2008 and for the sake of brevity are summarized herein. Briefly, Tanaka teaches lyophilized compositions comprising hepatocyte growth factor (also known as HGF), a stabilizer, sodium chloride, buffer, and a surface active agent. Phosphate is preferred as a buffer, and the osmotic pressure ratio is to be maintained so that the reconstituted HGF is suitable for injection. Tanaka teaches that pH 5.0 to 6.0 is particularly preferred, and the reference also teaches inclusion of surface active agents in general and a polyoxyethylene ether surface active agent in particular. Tanaka also teaches using vials to prepare the lyophilized compositions. Tanaka teaches that amino acids in general can be used as stabilizing agents, however Tanaka does not teach inclusion of the specific amino acids recited in claims 1 and 3 as the stabilizing agent.

Yamahira teaches that addition of polar amino acids to solutions comprising protein prior to their lyophilization is sufficient to increase their stability following lyophilization. Yamahira specifically recites arginine, glutamic acid, and histidine as among the most preferred stabilizing amino acids. Arginine and histidine are taught by Yamahira to have superior ability to stabilize lyophilized protein solutions. However, while Yamahira teaches lyophilized preparations comprising a protein and the specific amino acids as stabilizing agents, the reference does not teach a preparation comprising HGF, as required by independent claims 1 and 3.

It would have been obvious to one of ordinary skill in the art to modify the invention of Tanaka by selecting any of the polar amino acids taught by Yamahira as the stabilizing agents, with a reasonable expectation of success. The motivation to do so would be to choose an amino acid known to be effective in stabilizing lyophilized preparations. Tanaka teaches that amino acids in general are suitable as stabilizing agents, and Yamahira guides the artisan to selection of the polar amino acids in general, and arginine and histidine in particular, as the patent shows that they are superior in stabilizing the protein following lyophilization.

In the remarks filed 11 March 2009, applicant traversed the examiner's determination of obviousness. Specifically, applicant argues that:

1) the Office has failed to establish a prima facie case of obviousness, as the present invention is an improvement over that of Tanaka;

2) there would be no motivation to combine the teachings of Tanaka with those of Yamahira, since the teachings of Yamahira are limited to urokinase and not generally applicable to proteins.

Applicant's arguments have been fully considered but they are not persuasive. With respect to 1), applicant argues that the presently-claimed composition has improved properties relative to the compositions disclosed by Tanaka. The examiner does not contest that certain improved properties may in fact be present in the compositions comprising the specifically recited amino acids. However, this does not change the examiner's conclusion that the claimed invention would have been obvious to one of ordinary skill in the art. Tanaka specifically teaches that a stabilizer should be included in the lyophilized composition and points to amino acids as being particularly preferred stabilizers. While Tanaka does not list the amino acids recited in the present claims, Yamahira indicates that many of these amino acids in fact are suitable as stabilizers in compositions comprising lyophilized proteins. Thus one of ordinary skill in the art would have had a reasonable expectation of success in substituting the stabilizing amino acids taught by Yamahira for those used in the methods of Tanaka.

Applicant also argues that the compositions from Tanaka are prepared at a high concentration and use citric acid as a buffering agent, both of which are contrary to the present invention. The examiner disagrees with applicant's characterization of both the present claims and the prior art reference. First, it is noted that Tanaka teaches preparing the lyophilized composition from a solution of 10 mg/ml HGF. While claims 1 and 3 recite the limitation "which is prepared from an aqueous solution containing the [HGF]… at a concentration lower than 5 mg/ml", this is a product-by-process limitation which describes one way to make the product. Absent evidence that a product made from a higher concentration is patentably distinct, the limitation does not receive patentable weight. Applicant argues that certain examples set forth in the specification provide evidence of the superior nature of the claimed invention, but none of those examples explicitly compare the properties of lyophilized compositions prepared from 10 mg/ml solutions with those prepared from solutions at a concentration lower than 5 mg/ml as claimed. Additionally, Tanaka specifically guides an artisan of ordinary skill to select a concentration such that following reconstitution, the osmotic pressure will be suitable for injection; see for example paragraph [0020]. Furthermore, with respect to the argument that Tanaka's citric acid is not suitable, the examiner notes that nothing in independent claims 1 and 3 excludes citric acid; all that is required is "a buffering agent", which can include citric acid

buffers. Note that acidic compositions are clearly considered appropriate; see for example claims 10 - 11, drawn to acidic (pH < 7.0) compositions. Additionally, Tanaka explicitly teaches that phosphate buffers, encompassed by present claim 7, can be used. So even if the claims were limited to compositions that comprise phosphate buffers, such claims would still have been obvious to one of ordinary skill in the art, given that Tanaka teaches this is an appropriate buffer for use in making lyophilized HGF compositions.

With respect to 2), the examiner disagrees with applicant's interpretation of the reference by Yamahira. While urokinase is the only protein discussed in Yamahira, there is no reason to believe that the teachings of the patent, specifically which compounds are suitable for increasing stability of a lyophilized protein, are so limited as to only apply to this one particular protein. An artisan of ordinary skill clearly would have looked to determine which other stabilizing agents, including amino acids as taught by Tanaka, could be substituted in the solutions. Since Yamahira in fact provides guidance as to which amino acids work as stabilizing agents, selecting any of those disclosed by Yamahira would not have been the result of a non-obvious discovery deserving of a patent, but of routine experimentation.

For the reasons above and those previously made of record, the rejection under 35 USC 103(a) stands.

Conclusion

5. No claim is allowed.

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Bernardi et al., U.S. Patent 3,629,305, issued 21 December 1971. The patent teaches that including amino acids, such as arginine or lysine, increases the stability of estrone sulphate; see for example column 1 lines 45 - 57.

B) Gits et al., U.S. Patent 4,053,583, issued 11 October 1977. The reference teaches that including arginine in a lyophilized composition improves the stability of the composition. Gits used arginine to increase the stability of lyophilized virus for long-term storage; see column 2 lines 35 - 46.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
May 4, 2009